THE PTOMAINES OR ANIMAL ALKALOIDS

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THEIR RELATION TO DISEASE.

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ARTHUR P. LUFF, M.B., B.Sc. (Lond.),

LECTURER ON MEDICAL JURISPRUDENCE AND TOXICOLOGY, AND WARDEN OF THE COLLEGE, ST. MARY'S HOSPITAL; OUT-PATIENT PHYSICIAN TO THE NORTH-WEST LONDON HOSPITAL.

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Lecturer on Medical Jurisprudence and Toxicology, and Warden of the College, St. Mary's Hospital;
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THE discovery of the Ptomaines or Animal Alkaloids is so comparatively recent, and the probable relation that they bear to disease as causative factors of symptoms is but just dawning upon our minds, that I propose in this communication, which I intend to be a preliminary one to some researches that I am undertaking in connection with the subject, to briefly review the work that has been done in connection with these bodies, to summarize our present knowledge of them, and to consider their relation to certain diseases and the importance that a closer acquaintance with and a more accurate knowledge of the properties of these peculiar bodies may have on the treatment of those diseases in the future. For many of the facts contained in this paper I am indebted to the writings of Brieger, Gautier, Hugounenq, A. M. Brown, Sir W. Aitken, and Dixon Mann.

I propose to discuss the subject under the following three heads :—(I.) What are the ptomaines or animal alkaloids? (II.) From what substances and under what conditions are they formed? (III.) What is our present knowledge of their relation to disease, and how may a further and more complete acquaintance with them influence the treatment of disease in the future?

(I.) Ptomaines are alkaloids produced by the decomposition of animal substances. By the term *alkaloid*, as generally employed, is understood *an organic base derived from a vegetable source;* by the term *ptomaine* or *animal alkaloid*, we are to understand *an organic base derived from an animal source.* The word *ptomaine*, which is derived from Πτωμα, a corpse or dead body, and *inus*, belonging to, was at first restricted to alkaloids produced by cadaveric decomposition, but it is now also employed to designate alkaloids of animal origin formed during life as a result of chemical changes induced by some agency or other acting within the organism. The term *leucomaine* has recently been introduced to particularize the animal alkaloids formed during life from those produced by decomposition of dead animal matter. I shall not, however, in this paper, use that term, as the name ptomaine is more familiar, and, moreover, it is probable that in the near future the terms *ptomaines and leucomaines* will be dropped, and that these bases of animal origin will be classed in one category as *animal alkaloids.*

(II.) At the beginning of this century, the formation of alkaloids by plants was clearly established, but until 1872 the power of manufacturing alkaloids was believed to be restricted to plants and not to be shared by animal organisms. The first faint foreshadowing of the production of alkaloids by animal substances occurred in 1820, when Kerner pointed out the resemblance between

the symptoms of poisoning by sausages and by atropine. In 1822, Gaspard and Stick extracted a venomous principle from corpses. In 1856, Panum detected a very active poison, which was neither albumenoid nor alkaloid, in putrid matter. In 1866, Dupré and Bence Jones found an alkaloidal substance, resembling quinine in some of its properties, in the liver. In 1868, Bergmann and Schmiedeberg obtained from putrid beer a nitrogenous crystalline substance, which they called *sepsine*, and which was subsequently thought to be discovered in septicæmic blood. In 1870, Gautier, in France, commenced his researches on putrefying albuminous substances. A little later, Selmi, in Italy, examining the dead body of a person supposed to have been poisoned, extracted an alkaloid which he was unable to identify with any known body, and was led to suspect that it had been produced after death. In 1877, Selmi announced that by subjecting pure albumen to putrefaction he had been enabled to produce and separate two new alkaloids. Since then Gautier has made a series of elaborate and prolific researches, as the result of which several animal alkaloids have been discovered. To Gautier is due the honour and the credit of being the first one to demolish the artificial barrier that had been erroneously interposed between the physiological phenomena of the animal and vegetable kingdoms, and to clearly establish the doctrine that plants possess no monopoly, no exclusive power to manufacture alkaloids. Creatinine, xanthine, hypoxanthine, guanine, carnine and betaine, all genuine alkaloids, were found in the tissues of animals or in their excrementitious products.

Creatinine, discovered in urine by Liebig and Pettenkofer, was the first body of animal origin acknowledged to be an alkaloid. Later on, Liebrich detected the already known vegetable alkaloid betaine, in normal urine. In 1880, Pouchet detected carnine in the urine of man, and this was confirmed in 1881 by Gautier, who

showed that it possessed the general properties of a ptomaine. In 1882, Bouchard demonstrated that not only were alkaloids present in appreciable quantities in normal urines, but that they augmented notably in the course of certain maladies, typhoid fever, for instance; and later, Lepine and Aubert concluded that these alkaloids in the urine increase in quantity until the crisis of a disease is reached, after which they diminish (no alkaloid, however, was isolated in connection with any disease in sufficient quantity or sufficiently pure to admit of its ultimate composition being determined). Since then, Gautier, as the result of his investigations, has affirmed, that the incessant production of alkaloids at the expense of albumenoid materials is a function of all the animal tissues, and is an essential concomitant of the vital phenomena of all living things, animal and vegetable.

It is albumen, and I use this word in its widest sense, that we must regard as the common ancestor of alkaloids, whether animal or vegetable. Now, what is it that brings about these changes in the albumen molecule, that revolution amongst its constituent atoms, as the result of which follows the re-arrangement of its atoms into other bodies, among which are the ptomaines? The force necessary to effect these changes in the albumen molecule seems to be in many cases, though not necessarily in all, a force intimately associated with living matter, whether animal or vegetable, for even in the case of the corpse alkaloids, the ptomaines produced by decomposition of animal matter after death, these are formed as the result of changes induced by the vital activity of micro-organisms which set up cadaveric putrefaction. The changes induced in the albumen are such that the complex albumen molecule is split up into several less complex molecules, among which are the animal alkaloids.

The following is a list of the principal ptomaines that

have been extracted from putrefying animal matters and submitted to ultimate analysis :—

Collodine, $C_8H_{11}N$, from putrefying horseflesh and mackerel.

Parvoline, $C_9H_{13}N$, from putrefying horseflesh and mackerel.

Unnamed base, $C_{10}H_{15}N$, from putrefying fibrin of bullock's blood.

Hydrocollodine, $C_8H_{13}N$, from putrefying horeflesh and mackerel.

Putrescine, $C_4H_{12}N_2$, from human corpses.

Neuridine, $C_5H_{14}N_2$, from human corpses, and from putrefying fish and cheese.

Cadaverine, $C_5H_{16}N_2$, from human corpses.

Neurine, $C_5H_{13}NO$, from cadaveric putrefaction.

Muscarine, $C_5H_{13}NO_2$, from putrid fish.

Choline, $C_5H_{15}NO_2$, from cadaveric purefaction.

Gadinine, $C_7H_{16}NO_2$, from putrid cod-fish.

Recently Vaughan, in America, has extracted a ptomaine named *tyrotoxicon*, from decomposing cheese, milk, and cream.

But, as I previously stated, not only are alkaloids produced from albumen by its putrefactive decomposition, but also by the chemical changes occurring within the organism during life. In my opinion, the formation in the human economy of animal alkaloids will, in all probability, explain the genesis of many diseases. But not only in connection with disease, but every instant of our lives are alkaloids being manufactured within us as a result of the chemical changes upon which life is dependent. Gautier has shown that animal alkaloids are a necessary product of vital physiological processes, poisonous alkaloids having been extracted by him from the secretions of living beings, and from fresh animal tissues.

The following is a list of the principal animal alkaloids so obtained :—

Creatinine, $C_4H_7N_3O$, from urine.
Pseudoxanthine, $C_4H_5N_5O$, from urine and flesh.
Sarkine, $C_5H_4N_4O$, from urine and flesh.
Xanthine, $C_5H_4N_4O_2$, from urine and flesh.
Crusocreatinine, $C_5H_8N_4O$, from fresh meat.
Xanthocreatinine, $C_5H_{10}N_4O$, from fresh meat.
Guanine, $C_5H_5N_5O$, from flesh and guano.
Carnine, $C_7H_8N_4O_3$, from fresh meat.
Betaine, $C_5H_{11}NO_2$, from urine.

Animal alkaloids have also been detected in the liver, brain, heart, lungs, spleen, and saliva of man; these, however, have not been submitted to ultimate analysis, but only recognised by their reactions with the general reagents for alkaloids. The poisonous effects of certain shell-fish (mussels, &c.) have been shown by Brieger to be due to a ptomaine which he has named *mytiloxine*, $C_6H_{15}NO_2$.

As I just stated, animal alkaloids are being incessantly produced within our bodies as a result of the normal physiological processes of life. Side by side with the manufacture and building up of fresh cell-materials must go the destruction of pre-existing cell-elements, and amongst the *débris* resulting from this destruction are animal alkaloids. These alkaloids are eliminated by the bowels, kidneys, liver, skin, and lungs, but if from any cause these eliminating organs fail to perfectly fulfil their excretory functions, then an accumulation of these alkaloids in the circulation occurs, and a toxic action is exerted by them on the nervous centres. In this way can be explained the headache resulting from constipation, and the more serious nervous symptoms resulting from deficient excretory action of the kidneys in certain diseases

of those organs. But it is not only on these excretory organs that we depend for the removal of these animal alkaloids. A powerful agent is at work, destroying them and helping to prevent their infecting and poisoning the being that gave them birth, in the oxygen of the blood, which is continually oxidizing them and burning them up, and it seems probable that this combustion, to a large extent, occurs in the liver (Dr. Lander Brunton has made the suggestion, which he bases on an observation of his own and on one of Mr. W. E. Green, of Sandown, that freshly secreted bile is not bitter, that the bitterness which we associate with bile is not an inherent quality of that secretion, but is probably due to bitter animal alkaloids absorbed from the stomach and intestines during digestion). With this new knowledge, can we wonder that health is so precarious a condition as we know it to be, when we see that from imperfect elimination, or from imperfect destruction, or from increased manufacture of these alkaloids, the human body is at the mercy of these fell poisons manufactured within its own recesses? If, the enunctories remaining sound, there is excessive production of animal alkaloids, but inadequate elimination—a condition which is obtained in all forms of over-exertion, as in a prolonged march—then accumulation of material elaborated in excess and imperfectly eliminated occurs, an auto-infection, a temporary poisoning of the system results, the poison affecting the nervous centres and producing the fever of over-exertion, the fever of prostration.

(III.) I will now discuss briefly the probable relation of animal alkaloidal poisons to the infectious fevers. Bacteriologists have traced, in the majority of cases, to each infectious fever some special micro-organism, which has by many been regarded as the *materies morbi*, the causative factor of the disease, though at the time of their discovery no explanation was offered as to how these micro-

organisms start their own special disease in the body they have invaded. Now, one explanation, which I have for some time entertained, is, that after the admission of these micro-organisms into the body, and provided they find the conditions suitable, they live and multiply, and that as a result or a residuum of their vital activity a powerful alkaloidal poison is produced, the toxicity of which is the cause of the symptoms of the disease. If so, each infectious disease would be the result of a fermentative decomposition of albuminous matter within the body, induced by a special micro-organism manufacturing its own peculiar poison for each disease.

But in many non-contagious diseases it seems probable that, without the intervention of micro-organisms, abnormal chemical changes may result in the formation of poisons which exert a toxic influence on the body within which they are produced.

Now, can any facts or experiments be adduced in support of these views? Yes, but they are meagre, as one would expect considering the primeval condition of this domain, but I think that they are prophetic. Pouchet has extracted from the fæces of a cholera patient an alkaloidal body, which injected into animals produces slowing of the heart, and later death, followed quickly by *rigor mortis*. The same author, and also Nicati and Rietsch, have obtained from cultivations of Koch's cholera bacillus traces of an alkaloid which appeared to be identical with the preceding one. Again, from cultivations of the typhoid bacillus Brieger obtained a small quantity of a poisonous alkaloid that he calls *typhotoxine*, and which yielded reactions different from the alkaloids he had previously isolated from putrefying animal matters. Quite recently Dixon Mann has extracted from the abdominal and thoracic organs of a patient dying of typhoid fever, during the third week of the attack, an alkaloid, which was

obtained in too small a quantity to enable its composition by ultimate analysis to be determined, but which by its qualitative reactions differs from the typhotoxine obtained by Brieger, although I think it is quite possible that the differences as regards the action of reagents might be caused by impurities or by changes induced in the alkaloid during extraction by one or the other worker. Dixon Mann has also extracted from the organs of a patient dying of septicæmia, of unknown origin, a small quantity of an alkaloidal poison. Again, Brieger from cultivations of the tetanus bacillus extracted four ptomaines, all of which when injected into mice produced tetanus.

Such is the state of our present knowledge of the relation of the animal alkaloids to the infectious diseases. It is true that it is but scanty, but it is the first gleam of light penetrating an almost Egyptian darkness in which the causation of the infectious fevers is enshrouded. It marks the commencement of the exploration of a dark continent of disease by the science of chemistry.

The tendency of modern medical science is to seek for an explanation of the phenomena that accompany disease, and not to relegate these phenomena to such vague and theoretical causes as perverted metabolism, disturbed action of nervous centres, &c. The question is, May not many of these phenomena be due to chemical processes occurring within the body? Shall we not, therefore, be proceeding in the right direction by endeavouring to ascertain (*a*) the causes that start these chemical processes, and (*b*) the actual products of these chemical processes and the properties of those products? If the treatment of disease resolve itself into a combat with definite chemical compounds, an accurate knowledge of the properties of which we have obtained, then the therapeutical treatment of disease will be based upon

much surer and more definite principles than the treatment of complex vital processes of whose nature we have but a vague and uncertain knowledge.

In my opinion, it is not so much in the body after death that we should search for these alkaloidal poisons, as in the excretions by which they may be eliminated, since on account of their probable instability they are extremely likely to have suffered decomposition under the influence of post-mortem changes. Granting that these poisons are produced during certain diseases, and are the causative factors of the symptoms of those diseases, then they must eventually either be destroyed within the body or eliminated in the excretions. It is, in my opinion, in the urine that careful research will most probably reveal the presence of these poisons. The nephritis produced so frequently in connection with certain fevers is probably due to the irritation of the kidney tissues by the poison during the act of elimination, just as cantharidin in being eliminated by the kidneys produces an inflammation of the kidney substance as a result of its irritant action.

If we become acquainted with these poisons and their properties, then the discovery of antidotes that could render them insoluble or innocuous would lead us to the direct treatment of the infectious fevers, and would constitute a great advance in medical science.